IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III, Sarwat Khattak, and Greg Randall		
Serial No.:	10/053,929	Art Unit:	1618
Filed:	January 22, 2002	Examiner:	Blessing M. Fubara
For:	*POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Julie Straub and Howard Bernstein, hereby declare that:

1. We are co-inventors of the above-identified application.

2. We conceived of and reduced to practice a method of forming microparticles that contain a diagnostic agent, which was subsequently described in U.S. Patent No. 6,565,885 to Tarara et al. This method involves spray drying a feed stock containing the diagnostic agent, a surfactant and a blowing agent. We conceived of and reduced to practice this method prior to September 29, 1997, as demonstrated by the attached copies of pages from a laboratory notebook (Exhibit A).

3. As noted in Exhibit A, the feed stock to the spray drying apparatus contained ammonium acetate, lecithin, (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25), D,L-

poly(lactide), and air. This composition was emulsified using a VirTis homogenizer to form an emulsion, which was then spray dried using a small-scale lab spray dryer (see Exhibit A, page 14). The resulting microparticles had diameters ranging from 1-20 microns and were hollow with internal central-like voids containing the air bubble, as demonstrated by transmission electron microscopy (see Exhibit A, page 116). These microparticles were echogenic (see Exhibit A, page 105, injection 7).

4. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 03 Mar 06 Julie Straub

Julie Straub

Date: 03 Mar. 06 Howard Bernstein

Howard Bernstein

450644116_1

EXHIBIT A

TITLE

Work continued from Page 13 Henry T. B[illegible]

PROJECT NO.

BOOK NO.

Investigator(s): H Brook Date:

Notebook/page #: Microsphere lot #: [illegible]

Microsphere Production

Process Room Conditions

Room Temp.:	22°C
Room Humidity:	51.5% RH

Polymer Preparation

Polymer type 1:	PEG-PLGA
Source & Lot no.:	BPI Lot # 504-12-29
Mass (g):	3.60 g
Polymer type 2:	D,L-PLA
Source & Lot no.:	BPI Lot # 38038
Mass (g):	3.6 g
Solvent Type:	MeCl2
Source & Lot no.:	EM, lot no 35068
Volume:	240 mL
Surfactant type:	Lecithin
Surf.(%w/vol):	25 mg
Dissolution Meth.:	Mixing
Dissolution Temp.:	Room temperature
Dissolution Time:	12:55
Excipient 1:	H_2O
Source & Lot no.:	House DI
Amount, g/mL:	8 mL

Comments:
Dissolve ammonium acetate in water as follows:
10.8 g in 8 mL of H.D. Add 8 mL to polymer solution.

Spray Conditions

Cleaning Proc.:	Vacuum and acetone, MeCl2 rinse [illegible]
Nozzle type:	0.7 mm standard, unit B
Gas Pressure:	95 psi
Gas Flow rate:	600 L/h
Gas type:	N2 medical grade
Feed Flowrate:	112 rpm
Inlet Temp.:	50°C
Start Time:	1:16
Finish Time:	1:28
Mass Recovd:	18.68 - 16.71 = 1.97
Yield (%):	27%

Process Conditions:	Start 1:17	Middle 1:27	Finish
Outlet Temp.:	29°C	28°C	29°C
Filter vacuum:	-40 mbar	-39 mbar	-38 mbar

Comments:
Did not tape inlet tube as I had done on previous batches

Aeration Methodology

Sonication:	None
Horn type:	
Frequency:	
Power:	
Temperature:	
Time:	
Time until spray:	
Sparging:	None
Gas type:	
Gas pressure:	
Temperature:	
Time:	
Time until spray:	
Homogenization:	VIRTIS
Blade type:	macro ultra-fine generator
Time:	minute [illegible]
Speed:	20,000 RPM
Temperature:	In bath
Time until spray:	~1 minute

Comments:

Drying Methodology

Type:	Lyophilization, VIRTIS Freezemobile
Total dry time:	Start [illegible] [illegible], [illegible] [illegible]
Mass recovered:	[illegible] 18.485 - 16.71 = 1.78 g
Yield (%):	13.98 [illegible] 25%

Comments:
[illegible] in [illegible] at [illegible], removed from dryer at 2:35 [illegible], weight = 18.49; placed back on lyophilizer. Removed from lyophilizer at 10:50 am, [illegible].

Sizing Methodology

Room Temp.:	
Room Humidity:	
Screening Time:	
Screen sizes:	
Screen type:	
Product recovered:	
Yield (%):	

Comments:

Henry T. B[illegible]

SCIENTIFIC NOTEBOOK [illegible]

Work continued to Page 15

SIGNATURE Henry T. B[illegible] DATE

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80 TITLE TJU Study For 4

PROJECT NO

Thomas Jefferson University [illegible] Experiment [illegible]

Confidential

Sample ID	Material	Vehicle	mg/mL [illegible]	Volume Injected (mL)	Final mg/mL	Suspension Preparation Comments	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	NA	X		
[illegible]	[illegible]	VI	0	10	0	X		
[illegible] [illegible]	[illegible] [illegible] mg	VI	[illegible]	10	0.17	176.2 mg		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.50	615.3		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.50	612.2		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.50	~~mg~~ 614.1		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.50	~~612.3~~ 612.4		

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Sample ID	Material	Vehicle	mg/mL [illegible]	Volume Injected (mL)	Final mg/mL	Suspension Preparation Comments	[illegible]	[illegible]
[illegible] [illegible]	[illegible] 300 mg	water	50	2	0.1	X		
[illegible] [illegible]	[illegible] 100 mg	water	50	2	0.1	X		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	610.4		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	617.8		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	612.3		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	421		

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Sample ID	Material	Vehicle	mg/mL [illegible]	Volume Injected (mL)	Final mg/mL	Suspension Preparation Comments	[illegible]	[illegible]
[illegible] [illegible]	[illegible] 300 mg	water	50	2	0.2	X		
[illegible] [illegible]	[illegible] 300 mg	water	50	2	0.2	X		
[illegible] [illegible]	[illegible] 300 mg	water	50	2	0.2	X		
[illegible] [illegible]	[illegible] 300 mg	water	50	2	0.2	X		
[illegible] [illegible]	[illegible] 200 mg	water	50	2	0.2	X		
[illegible] [illegible]	[illegible] 200 mg	water	50	2	0.2	X		

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Sample ID	Material	Vehicle	mg/mL [illegible]	Volume Injected (mL)	Final mg/mL	Suspension Preparation Comments	[illegible]	[illegible]
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	617.2		
[illegible] [illegible]	[illegible] 600 mg	VI	50	10	0.5	606.8		

Jud

Samples weighed by Howard in Dry Box on [redacted]. All but the 94/082 and 94/083 Samples sent to Forsberg on [redacted] by Air Borne on dry ice / gel pak

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DATE [redacted]

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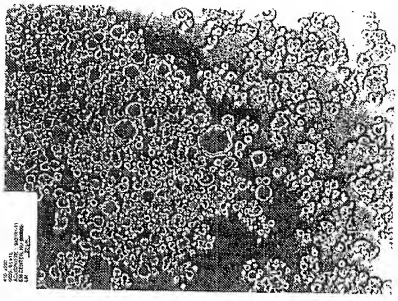
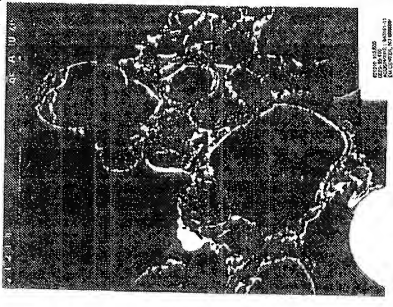
DATE [redacted]

WITNESS

DATE

115





SCIENTIFIC SUNDRY PRODUCTIONS CHICAGO 60605 Made in USA

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DATE

106 TITLE PROJECT NO

Acusphere

Notes

All samples will be prepared by vortexing and sonication.

All samples will be preweighed in 20 mL scintillation vials. Empty 20 mL scintillation vials will be brought.

Saline (0.9%) will be used instead of water for the bulk diluent in the pumping system. Preweighed samples of 16.2 g of NaCl will be brought out, and mixed to 1800 mL with water in a bottle. Two such bottles will be sent to TJU. A total of 20 NaCl vials will be brought.

Vehicle 1 = 0.5% Tween 20, 3% glycerol ← Never used

Vehicle 2 = 0.5% P127, 54.6 mg/mL mannitol

1) System essentially same as 8/3/95 experiment, except 500 mL saline in body
2) Vehicle 2 (VF) was used
3) Yongze Wu did the entire study
4) After injection of sample, sample was stirred, flow rate was then increased to 500-800 mL/min until echogenic material detected by the oscilloscope, Flow rate then dropped to 100-200 mL/min.
5) The "latex window" moved dramatically with each pulse
6) Tubing was manipulated to remove bubbles. At least once (prior to injection 9) this resulted in change of alignment. At that one detected time, the machine was realigned.
7) Cleaning procedure: (1) water pumped to remove all material, then saline pumped in (2) water emptied, saline added + pumped through.

(2) System pumped dry, saline pumped in

[illegible]

SCIENTIFIC BINDERY PRODUCTIONS CHICAGO Made in USA

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TITLE

Work continued from Page

80/84 105

Acusphere [redacted]

Confidential

94050-37

Injection #	Sample ID/Material (Vehicle, mL)	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	Spleen (?)
1	1-Albunex 0.4	NA (4ml saline, 1x syringe)	none ~ 15 sec, echogenic during sample		no
2	1-Albunex 0.5ml	NA (1x p inject)	little gas echogenic during sample		no
3	1-Albunex 0.7	"	echogenic		[illegible]
[redacted]	2-Vehicle (F) 10	V/S3/V	inject [illegible] not echogenic		no
[redacted]	3-VF-12ml	V/S1/V flakes/	a little echogenic	too little to follow	yes
[redacted]	4-VF-12ml	V/S1/V/S1/V flakes	a little echogenic ~ 3 sec	decrease over 1 min	yes
[redacted]	5-VF-12ml	V/S1/V few flakes	echogenic (bubbling)	V [illegible]	yes
[redacted]	94050-9 (US 3ml) Sh	4ml	echogenic 25 sec [illegible]	< 1 min	yes
[redacted]	94050-11 (US 3ml) Sh	4ml	a little [illegible]	< 1 min	no
10	Albunex 0.7ml	NA (saline in pun)	strongly echogenic [illegible]	[illegible]	yes
11	94050-7 (VF)	V/S1/V/S1/V flakes	less - bubbles [illegible]	not long	[illegible]
12	18-VF-12	V/S1/V a few flakes	slightly echogenic	~ 2 min	yes
13	19-VF-12	V/S1/V/S1/V a few flakes	none		yes
14	13-2ml H2O	Sh 2ml	echogenic [illegible]	1-2 min	yes
15	15-2ml H2O	Sh 2ml	echogenic ~ 3 sec	1-2 min	yes
16	8-(4ml H2O) Sh	4ml	echogenic 3 sec	1-2 min	yes

Acusphere [redacted]

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Injection #	Sample ID/Material	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	
	55				
17	5 (suspension)	particles suspension 1ml V/S1/V/S1/V	slightly echogenic	gone 1-2 min	yes
18	6-VF-12	a few flakes V/S1/V/S1/V	none		[illegible]
19	8-VF-12	a few flakes V/S1/V/S1/V	none		no
20	11-VF-12	a few flakes V/S1/V/S1/V	slightly echogenic	< 1 min	yes
21	10 2ml [illegible]	Sh 4ml	very very slight	< 1 min	no
22	12 2ml [illegible]	Sh 4ml	very very slight	< 30 s	[illegible]
23	21-VF-12	V/S1/V/S1/V 10ml	very very slight	< 30 s	[illegible]
24	14 4ml H2O	Sh 2ml	none		no
25	17-VF-12ml	V/S2/V 10ml	none		no
26	Albunex 0.7	NA	a little echogenic		
27					
28					
29					
30					
31					
32					

Study Run # TJU [illegible]

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DATE [redacted] WITNESS

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